Responses to Peer Reviewer Comments

US PHS Preexposure Prophylaxis for the Prevention of HIV Infection in the US – 2013: A Clinical Practice Guideline and

US PHS Preexposure Prophylaxis for the Prevention of HIV Infection in the US – 2013: Clinical Providers' Supplement

19 November 2013

In compliance with the Peer Review Plan (available at http://www.cdc.gov/hiv/strategy/planning/pdf/PRP%20PrEP.2.pdf), we provided draft documents listed above to selected independent peer reviewers. In addition, each peer reviewer was provide a copy of the summary of comments received from public presentation of key guideline recommendations on a series of webinars (available at (http://www.cdc.gov/hiv/pdf/policies_responses_draft_clinical_practice_PrEP_us.pdf)

We requested expert opinion from the peer reviewers on:

1. Whether any studies on which the recommendations were based were inappropriate as supporting evidence or were misinterpreted
2. Whether there are significant oversights, omissions or inconsistencies that are critical for the intended audience of clinicians
3. Whether the recommendations for the intended audience of clinicians are justified and appropriate
4. Any other comments

Listed below are comments received from the peer reviewers and our responses**.**

1. Were any studies on which the recommendations were based inappropriate as supporting evidence or misinterpreted?

Reviewer #1

No comments requiring a response

Reviewer #2

All of the data are discussed accurately, but there are some places where the emphasis or wording could be changed to help in interpretation of the results. I would recommend that:

a) TDF-2 limitations be discussed up front (rather than just in the table)

Accepted and text edited accordingly

b) Fem-PrEP be stated as not finding efficacy, rather than as having efficacy of 6% that didn't reach statistical significance

Accepted and text edited accordingly

c) Phase 2 studies do not discuss effect on incidence (particularly the FHI African study, given the numerous problems with that study)

For transparency, we include all phase 2 and 3 PrEP trials with accompanying GRADE quality of evidence ratings.

d) Some caveats be included in discussion about "efficacy" as estimated by drug levels, given that these are all modeled results that do not take advantage of randomization, and thus are particularly susceptible to bias

Footnote added to Table 3

e) HPTN 052 does not include data on transmission between men; this could be highlighted in your discussion of these results, as well as the potential for different results in populations with multiple partners (and the risk for HIV acquisition outside of main partnerships)

The absence of data on transmission between men was added. A fuller explanation of results from the HPTN 052 trial is beyond the scope of this document.

f) Data on intermittent PrEP in Africa suggest that when less than daily dosing is prescribed (e.g., 2x/week or coitally dependent), adherence is even worse. This point could be made more clearly.

Accepted and text edited accordingly

g) Page 14. [Fem-PrEP results]]. This makes it sound as though there was a true reduction in risk, but just not statistically significant. My read of this study is that there was no difference between groups, not that there was a modest reduction that didn't achieve significance. Is this [analysis of pregnancy rates] included to suggest that there were not significant differences in unprotected sex between groups? If so, that might be added to be explicit about why this is included.

Accepted and text edited accordingly

h) Page 17. [Table 2. Evidence Summary Tables – HIV Incidence Findings]. Probably clearer for the average reader to have this column list efficacy, rather than both HR and efficacy.

Noted. For completeness of data reporting, we have not changed the table.

i) Why were incidence results per arm presented for some trials, but not the others?

Table content reviewed. Some studies did not publish infections per 100 person-years so no entry is provided on the table.

j) Page 18. [Table 3. Measures of Efficacy by Medication Adherence]. I think it is important to explain that all other estimates take advantage of randomization (comparison of active vs. placebo arms) but that just looking at levels in blood only looks at one arm (active) and may therefore be subject to bias (as those who become infected may be different in many ways from those who remain uninfected).

Table footnote added

Reviewer #3

a) Page 12. Cannot be "both study groups" the study had 3 study arms. The sentence should be re-worded along the lines "in the medication (or TDF and TDF/FTC) groups…"

Accepted and text edited accordingly

Reviewer #4

a) In your table 1, I have problems with the limitations column. You might consider subdividing it into adherence, retention power. When you have high lost to FU fundamentally you have an adherence problem –and a failure from an ITT perspective. One might also suggest whether drug levels were done that might enhance the quality.

Information about the method of applying the GRADE criteria for upgrading and downgrading the quality of evidence in the summary table was added both as a footnote to Table 1 and in Appendix 2.

Reviewer #5

No comments requiring a response

Reviewer #6

No comments requiring a response

2. Are there significant oversights, omissions or inconsistencies that are critical for the intended audience of clinicians?

Reviewer #1

a) HIV Testing Page 25. We could also advise patients to come sooner to get HIV tested and talk about PrEP if adherence for some reason is not ideal- it is crucial to build trusting relationship with patients so they feel comfortable bringing up any issues.

Text reviewed. No change indicated. This guideline does not prevent clinicians from additional testing based on their clinical judgment about specific patients in their care.

b) Pages 32-33. Do these guidelines plan on recommending liver function testing at any interval?

No, because there is no evidence from the PrEP clinical trials with TDF or TDF/FTC to suggest that monitoring liver function is necessary for patient safety (See Truvada package insert). This guideline does not prevent clinicians from additional testing based on their clinical judgment about specific patients in their care.

c) If high risk, I would recommend STI screening/testing or at least assessing behaviors for potential STIs and testing if necessary every 3 months.

Text reviewed. The guideline and supplement already include recommendation for assessing risk behavior at each 3 month visit. No change made in the recommended frequency of STI testing (remains every 6 months). This guideline does not prevent clinicians from additional testing based on their clinical judgment about specific patients in their care.

d) I would think this [evaluation for need to continue PrEP] should be done at every visit (every 3 months)

Noted. No change made. This guideline does not prevent clinicians from additional evaluations based on their clinical judgment about specific patients in their care.

e) Patient/Provider Checklist (Provider Section). Include STI testing?

Accepted and Checklist revised accordingly.

f) Patient should have a way to reach the provider- can call clinic if any questions arise, or for any issues that come up-I think establishing good two-way communication is key to adherence.

A space is present on the patient portion of the checklist for this information to be entered.

Reviewer #2

a) Given the "confusion" that many have expressed about what the field of studies is telling us about PrEP's efficacy for women, I think it would be helpful to include a section that discusses what we currently understand about efficacy in women. I think PrEP should be encouraged for consideration in serodiscordant couples, particularly if the HIV partner is not on treatment. I think the questions about whether the "discordant" results from TDF-2 vs. Fem-PrEP and VOICE could be summarized as being about: a)adherence, b) Susceptibility (e.g., age, STI's, inflammation), c) Infectiousness of partner (e.g., multiple partners, some of whom likely have higher VL and/or lower CD4 counts than in the Partners PrEP study), d) Other factors.

Recently published results of the VOICE study have been added as well as a reference that discussed the known/unknown factors related to different efficacy results in trial that included women.

b) Providers may want to discuss this with their patients when deciding on whether or not to prescribe PrEP, and how to discuss likely efficacy.

Noted. No change indicated.

c) In the section on nPEP (page 37), please be sure that if repeated exposures have occurred in someone presenting for PEP, that infection is ruled out before beginning PrEP.

Accepted and text edited accordingly.

d) Page 15. [boxed statement: two present strong evidence of efficacy]. In the table, TDF2 is characterized as having moderate evidence, based on retention issues and relatively small number of endpoints.

Accepted and text edited accordingly.

e) Consider how to incorporate Project AWARE data when that is available.

This text will be reviewed and edited when data is published from the Project Aware trial.

f) It would be helpful to include a specific discussion of risks of resistance. The data suggest that if PrEP is taken regularly, efficacy may be high (and therefore resistance low); conversely, if adherence is poor, resistance may also be uncommon, as the drug is not being taken. However, if taken intermittently, resistance potential could be high.

This text was reviewed and a recent publication added.

Reviewer #3

a) Page 33. Practical issue/question of when sexual activity can commence post initiation of PrEP should be addressed----the time window from screening to initiation---would suggest a minimum of 72 hours if only extrapolating from the STRAND trial data.

As there is no trial data directly answering this question, we have not addressed it in these guidelines.

b) Page 38. Guidance as to how one might transition from nPEP to PrEP is needed. Would strongly consider PCR post the 28 day PEP regimen prior to initiating PrEP

Text was reviewed and edited to clarify that acute infection needs to be ruled out before initiating PrEP in this context.

c) Page 27. Although clinicians must be vigilant to the symptomatology of acute HIV seroconversion, the clinician should alert the patient to these signs and symptoms as well.

Noted. This information is included on the patient/provider checklist and the patient handout on Acute HIV infection (both in the Clinical Providers" Supplement).

d) Page 30. As written these appear to be goals—rather than a single goal, therefore either change "acquisition of HIV infection and its resulting.." to " acquisition of HIV infection with its resulting.." or make it: "The goals of PrEP are….".

Text was reviewed and edited accordingly.

e) The clinicians are not the ones initiating the medications

Text was reviewed and edited accordingly.

f) [Add a bullet]: Education/inform those prescribed PrEP (and potential PrEP candidates) on the signs and symptoms of acute HIV seroconversion.

Noted. This information is included on the patient/provider checklist and the patient handout on Acute HIV infection (both in the Clinical Providers" Supplement).

Reviewer #4

a) In the clinician's guide where you describe the various trials and with the VOICE trial complete it would be good to add this as well.

Recently published results of the VOICE, Bangkok Tenofovir Study, and US MSM Safety trials have been added.

b) P23 2nd para last sentence. Self report by individuals is generally a poor marker for any consistent behavior. Not sure this should drive whether other prevention methods should be provided.

Noted. No change made as this is the adherence measure most available and used in clinical practice.

c) P 24 Box B1 and B2, 4th bullet. Not in a monogamous relationship suggests that if a person thinks they are in a monogamous relationship may not need PrEP. However, there are good data indicating that knowledge about being in such a relationship is far from accurate. Indeed, many of our women who are infected thought they were in a monogamous relationship.

Noted that this is not a perfectly sensitive criterion. No change made.

d) The last bullet of Bx B2 says "infrequently uses..". The concept of frequently is a relative one and as such I would avoid this "greyness" in the recommendation.

Noted. However, adequate data iare not available to make a more quantitative statement. No change made.

e) P25 in HIV testing section. I do not see any test for DNA/RNA at intiation. We are seeing positives on this at study enrollment and since there is only quarterly FU a patient might be infected on drug for months.

Several options for detecting acute HIV infection are presented (Figure 1), including antigen assays.

Reviewer #5

a) On page 31, you provide drug interaction info for opiate antagonists, but don't recommend PrEP for IDU. Seems strange to highlight these drugs without mentioning other agents that are used to treat

substance use, like naloxone, and maybe you want to include psychotropic agents since many potential PreP users may have other behavioral health issues.

The results of the Bangkok Tenofovir Study with IDU were recently published and the clinical practice guideline has been revised to include a recommendation for PrEP use by IDU. In addition, the text has been edited to reflect additional safety and preventive health issues for PrEP in this population.

b) On page 15: the data on VOICE results needs to be updated, and since the Thai IDU PrEP study will be presented at the IAS 2013 meeting in Kuala Lumpur next month, it should be included.

Recently published results of the VOICE, Bangkok Tenofovir Study, and US MSM Safety trials have been added.

Reviewer #6

a) Of course the Voice study TDF/FTC arm findings are not included since they were released more recently. The addition of those data would not add much given the findings from the VOICE TDF oral and topical gel arms and FEM-PREP, nonetheless it will be an important addition for completeness.

Recently published results of the VOICE, Bangkok Tenofovir Study, and US MSM Safety trials have been added.

b) I did not note any glaring omissions but I did note that there was little discussion of the use of combo Ag/Ab tests to minimize the possibility of missing acutely infected persons when starting PREP. There is mention of the availability of these tests in the appendix but not in the text or Figure 1. I assume the thought is that these tests are not POC nonetheless I think they are worth mentioning.

Several options for detecting acute HIV infection are presented (Figure 1) including antigen assays In addition, the HIV assay tables (Appendix 1) have been updated.

3. Are the recommendations for the intended audience of clinicians justified and appropriate?

Reviewer #1

No comments requiring a response

Reviewer #2

a) I agree with the comment that it would be preferable not to use the term "at very high risk" as that can be stigmatizing. I recommend either "at risk" or "at substantial risk" (although I'm not sure why the latter is less perjorative, it seems to me that it is….)

Text was reviewed and the terms "high risk" and "very high risk" were replaced with "substantial risk" throughout the document.

b) The recommendation to not recommend PrEP for IDU should be altered to state that PrEP has not yet been demonstrated to protect against injection exposures. IDU may also be exposed through sexual routes, so it would be preferable to describe the behaviors that PrEP protects, rather than the group for whom it protects.

The results of the Bangkok Tenofovir Study with IDU was recently published and the clinical practice guideline has been revised to include a recommendation for PrEP use by IDU. In addition, the text has been edited to reflect additional safety and preventive health issues for PrEP in this population.

c) It would be helpful to have a single summary in which all of the important information (without all of the supporting data) are presented in a single place. This would be akin to the guidance document. As currently written, it seems that a provider would have to look in multiple places to find what s/he should do when considering and prescribing PrEP.

We have added a new figure summarizing this information in a format similar to earlier "interim guidance for PrEP" publications.

d) It is quite challenging to briefly summarize what constitutes high enough risk to consider PrEP. For MSM, it could be worthwhile describing the iPrEx inclusion criteria. Although the risk score is quite useful, there are situations (some given in my comments to the text) in which a patient could be misclassified. If the risk score is used, perhaps some caveats could be included so that the provider can tailor to the circumstances of the patient. For women, anal sex should also be included as a risk practice, particularly as condom use may be even less common with this practice (since contraception is not required).

Text reviewed. Anal sex added to HIV acquisition risk criteria for heterosexual women

e) I suggest that the recommendations include a 1-month check at initiation, to manage symptoms and adherence.

This is included in the text as an option for providers. These guidelines suggest an outer limit to the frequency of monitoring HIV status, adherence, and side effects (at least every 3 months) for safe use of PrEP. This guideline does not prevent clinicians from more frequent testing based on their clinical judgment about specific patients in their care.

f) Recommendations should explicitly discuss starting/stopping PrEP, and the need to return for HIV testing before "restarting" if patients stop on their own, but still have meds to restart.

Text reviewed and edited accordingly.

g) This [revision] may get at the issue that IDU can be exposed sexually. "PrEP is not ~~a~~ recommended ~~option for persons~~ *to prevent HIV acquisition* ~~exposed to HIV primarily t~~through injection drug use"

Following publication of the results of the Bangkok Tenofovir Study, a new recommendation for PrEP use by IDU is now included.

h) [suggested revision]. The risks and benefits of PrEP for ~~non-adult adolescents~~ *sexually active adolescents under the age of 18* should be carefully weighed in the context of local laws and regulations about autonomy for health care decision-making by minors.

Reviewed and no change made. Since the age of adulthood differs by jurisdiction, we will continue to differentiate "adults" and "non-adult adolescents" in this guideline for PrEP use to reduce both sexual and injection acquisition of HIV infection.

i) Intermittent can mean many things, including during periods of time. It would be reasonable for individuals at risk to use PrEP when having multiple sex partners, but they may discontinue during periods of monogamy with a negative partner. [suggested revision] "It is not recommended to prescribe PrEP to be used as less than a daily regimen (e.g., less than daily, ~~for intermittent~~, coitally-determined, or other noncontinuous daily use)."

Text reviewed and edited accordingly.

j) Include measurement [of renal function] at baseline [in key recommendation statement].

Text reviewed and edited accordingly..

<u>Reviewer #3</u>

a) Page 7. The recommendation is appropriately supported by the evidence provided by a well-executed Phase III, RCT, the iPREX study, with a validated and irrefutable laboratory endpoint: absence of HIV infection. The iPREX trial results indicate the consideration of oral PrEP in the form of the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg (TDF/FTC) should not be withheld as an HIV prevention strategy for sexually active MSM. Given the recommendation as written affords TDF/FTC to be "one prevention option"' for HIV prevention and that the current alternative and/or complementary HIV prevention strategies of condoms and abstinence have not and cannot be ethically subjected to RCT, the trial results effectively justify having the rating level of oral PrEP be a strong recommendation (IA) rather than its current moderate recommendation (IB) for the prevention of sexually-active adult MSM. The July 2012 FDA approval of TDF/FTC for its PrEP indication was "to reduce the risk of sexually acquired HIV-1 in adults at high risk" and not as the current recommendation reads at "very high risk". The

current recommendation should be aligned with the FDA indication language for TDF/FTC as oral PrEP accordingly.

Text of recommendation for MSM was reviewed. The terms "high risk" and "very high risk" were changed to "substantial risk" throughout the document. Change to IA recommendation being considered.

b) Page 7. The recommendation for oral PrEP for heterosexually-active men and women at risk for HIV acquisition is appropriately supported by the evidence provided by two well-executed RCT in heterosexual populations: the Phase III Partners PrEP and the Phase II TDF2. These two trials provide the appropriate and validated laboratory endpoint: the absence of HIV infection for the both the heterosexually-active adult male and female populations participating in these studies. Three other trials focusing exclusively on female heterosexuals: the Phase III FEM-PrEP, the Phase II TDF alone West African study and the as yet unpublished Phase III VOICE trial were all curtailed early and were unable to provide sufficient efficacy for oral PrEP when women were exclusively enrolled. The technical limitations and reasons for the three unsuccessful trials do not however uncut the results or validity of the Partners PrEP or TDF2 results supporting TDF/FTC as an effective HIV prevention strategy. In the present recommendation, TDF/FTC is endorsed as "one prevention option"' for HIV prevention, and as was noted in the previous recommendation, the current alternative and/or complementary HIV prevention strategies of condoms and abstinence have not and cannot be ethically subjected to RCT. The Partners PrEP and TDF2 trial results effectively justify having the rating level of oral PrEP be a strong recommendation (IA) rather than its current moderate recommendation (IB) for the prevention of sexually-active adult men and women. Once again, the July 2012 FDA approval of TDF/FTC for its PrEP indication was "to reduce the risk of sexually acquired HIV-1 in adults at high risk" and not as the current recommendation reads at "very high risk". The current recommendation should also be aligned to accord with the FDA indication language for TDF/FTC as oral PrEP.

Text of recommendation for heterosexual women and men was reviewed. The terms "high risk" and "very high risk" were changed to "substantial risk" throughout the document. Change to IA recommendation being considered.

c) Page 7. There are potential limitations and conflicts with this recommendation because of the variables involved: the gender of the HIV infected individual of the discordant couple, the 3 potential patients (father, mother and fetus) and the different goals and risks of conception and on-going or different sexual risk and activity during pregnancy and post-partum. The design and results of the Partners PrEP trial clearly demonstrate the efficacy of oral TDF/FTC as an HIV prevention strategy for the HIV negative partner in HIV discordant couples. The importance, relevance, design and results of HPTN 052 notwithstanding, as written, the current recommendation (unless it is premised under the concept of couples' counseling and both partners are monitored under the same clinician's care) does not afford sufficient guidance to the clinician for the HIV sero-negative individual under his/her immediate charge. Oral PrEP should be more than "discussed", oral PrEP

should be offered as one of the several options available to protect the uninfected partner. Given the multiple parameters and the data accrued the moderate strength of this IIB recommendation is appropriate, both the current recommendation and the accompanying text in the document at large would benefit from a more expository direction.

Text of recommendation for HIV discordant couples in the context of conception and pregnancy was edited accordingly. A factsheet to aid provider/patient discussion about PrEP use in this context was added to the Providers' Supplement.

d) Page 7. The efficacy and safety of oral PrEP for individuals directly exposed through injection drug use will await the results of the Bangkok Tenofovir study. However, the risk of HIV acquisition afforded those trading sex for drugs for example (Torian #) suggest the sexual activity is the more precarious risk behavior. Oral TDF/FTC as an HIV prevention strategy should not be withheld solely because of injection drug use.

Following publication of the results of the Bangkok Tenofovir Study, a new recommendation for PrEP use by IDU is now included.

e) Page 7 [use in non-adult adolescents]. This is prudent legal advice rather than specifically a medical recommendation. The available trials were all directed towards adults and have not included individuals under the age of 18 years of age.

Noted. No change indicated.

f) Page 7. The use of TDF/FTC combination without another effective ARV is inappropriate for either acute or chronic HIV infection. The use of the co-formulated agent alone in either circumstance is without RCT validity. All the available oral PrEP trials have actively attempt to exclude acutely and chronically HIV infected participants. The exclusion of acute and/or chronic HIV infection should be a priority because of the potential harm to both the individual and community at large for inciting resistance to either or both of the TDF/FTC PrEP components. The moderate strength of this current IIA recommendation negates the criteria of each of the RCT studies that lead to the FDA approval of TDF/FTC as PrEP. The data underpinning this recommendation merit its being a strong IA recommendation.

The text of this recommendation was changed and is being reviewed following publication of the results of the Bangkok Tenofovir Study with TDF alone as well as the finding of substantial efficacy for TDF alone among women and men in the Partners PrEP trial. Change to 1A recommendation is being considered. The guideline continues to emphasize exclusion of acute or chronic HIV infection as a requirement for prescribing PrEP.

g) Page 7. While other individual antiretrovrial agents, combinations and modalities may theoretically have biological plausibility as PrEP, they remain for the time being purely speculative as they await formal evaluation. No other agent can as of yet be recommended for PrEP at this time.

See response to f) above.

h) Page 7. Given the results of the HPTN 035 study on coitally-determined vaginal microbicides as PrEP, the current recommendation should read: "It is not recommended to prescribe *oral* PrEP for intermittent, coitally-determined, or other noncontinuous daily use."

Accepted and text edited accordingly

i) Page 7. The PrEP RTC protocols and DHHS guidelines support the underlying proposition that TDF/FTC is inadequate and inappropriate therapy for established HIV infection. The risks of developing ARV resistance are well known with inadequate therapy. The strength of the recommendation and the need to monitor the efficacy of PrEP as an HIV prevention strategy on a quarterly basis is readily supported by the current PrEP RCT data. The important logic underlying this recommendation may well be lost to the practicing clinician and should therefore be made explicit: "*TDF/FTC is inadequate therapy for established HIV infection*. HIV infection should be assessed at least every 3 months while patients are taking *TDF/FTC as* PrEP so that those with incident infection do not continue taking it *and engender resistance to either or both of its components".*

Accepted and text edited accordingly

j) Page 7. The PrEP RTC protocols and DHHS guidelines strongly support monitoring of renal function with any TDF-containing regimen.

Noted. No change indicated.

k) Page 8. Each and every sanctioned investigative trial of oral PrEP has included PrEP in conjunction with the known HIV prevention strategies appropriate to the given population under study. FDA approval of TDF/TFC as PrEP was predicated on its use "in combination with safer sex practices." The need to incorporate other effective prevention methods is underscored by the inability of TDF/FTC to prevent most other sexually transmitted infections. Both the successful and abortive PrEP RCT have faltered on the subject of adherence. The need for on-going adherence support measures and effective prevention methods is effectively underscored by this recommendation.

Noted. No change indicated.

a) In the summary for the recommendations I would like to return to one of the points that came up in one of the webinars in regards to testing of renal function. Considering that the goal is to prevent HIV in a generally healthy population I think we should err on the side of caution in regards to a 3m window (p32 for example). In this regard one might consider a UA for protein (Sherzer et al, AIDS 2012;26:867). The fact that certain SNP prevalence predisposes certain races/ethnicities to enhanced proteinuria may further confound a later testing time point (Tzur S, Wasser WG, Rosset S, Skorecki K. BMC Nephrol. 2012;13:142; Wasser WG, Tzur S, Wolday D, Adu D, Baumstein D, Rosset S, Skorecki K.J Nephrol. 2012;25:603). Since there exists considerable variability in GFR and kidney sensitivity to drug in terms of race, age, gender suggests this more conservative approach. In addition, since one is getting an HIV test there is no added inconvenience.

There is no evidence from the PrEP clinical trials with TDF or TDF/FTC provided to diverse populations in Africa, Asia, North and South America to suggest that monitoring for proteinuria in the absence of specific health conditions (e.g., diabetes), is necessary for patient safety. These guidelines, based on PrEP trial data, suggest an outer limit to the frequency of monitoring estimated creatinine clearance (at least every 6 months) among persons with normal renal function when initiating PrEP. This is the same frequency recommended for persons of all race/ethnicities taking tenofovir containing regimens for treatment of HIV infection. This guideline does not prevent clinicians from additional testing based on their clinical judgment about specific patients in their care.

Reviewer #5

a) I am not clear why PrEP for MSM was given a IB+ grading, which seems a little ambivalrent. After all, iPrEX was statistically significant, and the drug analysis by Anderson in Science Translational Medicine suggested greater than 90% efficacy when drug was detected. I do not know what a B+ means. Either embrace PrEP and give it an IA, or indicate your concerns about the existing data and give it a IB. I was also unclear why discordant couples got a lower recommendation that single heterosexuals given the powerful findings in Partners PrEP.

Text of recommendation for MSM was reviewed. Change to IA recommendation being considered.

Reviewer #6

No comments requiring a response

4. Other comments

Reviewer #1

a) Box A1 Male Risk Behavior Assessment (for MSM). I also ask about having unprotected anal sex with partners of unknown HIV status-casual partners or regular- if unknown, what would be the

chances that the partner is positive. We also find that in our patient population, alcohol consumption is a risk factor for unprotected casual sex among MSM/heterosexual- the type of substances used that may increase risk for unprotected sex may be different in different communities. Ask about history of STIs.

Box reviewed. No change made to box A1. Text of document recommends alcohol screening and Box B1 contains recommendation for STI testing

b) Box A2: Risk Behavior Assessment (for heterosexual men and women). Same comments I made above can be applied to heterosexual, Especially important is to ask about heterosexual anal sex, which we find to be common in our patient population (and it is many times, unprotected anal sex)

Text reviewed. Anal sex added to HIV acquisition risk criteria for heterosexual women

c) Pg 22. [in assessing the risk of HIV acquisition] I would also ask about history of herpes infection.

Noted. No changes made because we intent to provide a very brief set of questions to serve as the minimum.

d) Page 23. There are also innovative ways to promote HIV testing for partners (given they would not want to go to a healthcare provider or testing site), using the newly approved self-test HIV kits for example, and this could be part of the discussion with a healthcare provider. One recent study was a field trial study of actual use: 27 MSM used self-test with ~100 partners; 10 positive results (7 partners, 3 other); Sex did not occur after positive test. Ref: Use of a Rapid HIV Home Test Prevents HIV Exposure in a High Risk Sample of Men Who Have Sex With Men. Alex Carballo-Die´guez • Timothy Frasca •Ivan Balan • Mobolaji Ibitoye • Curtis Dolezal.

Noted. No change made to text because we are recommending that clinicians document HIV test results.

e) Page 33 TDM [therapeutic drug monitoring]. Issue of cost?

Noted. No change made because this is outside the scope of this document

f) Fact Sheets: I am sure that these patient information materials are most likely available in Spanish (and other languages), but I just wanted to mention it…

They have been translated into Spanish and will be made available during the implementation process.

<u>Reviewer #2</u>

a) Page 9. Can change the Grohskopf reference to the published one in JAIDS 2013

Accepted and reference edited accordingly.

b) Box A1. One issue is that the attributable risk associated with having multiple "negative" or unknown serostatus partners can be greater than unprotected sex with known positives. Also, although this is a focused history that will get you some of the most important risk information, in practice, it may be helpful (and less stigmatizing) to ask more open ended questions, and phrase the "without a condom" questions only after asking if they have had any of that type of sex, and explaining that sometimes condoms aren't used the entire time, or slip off or break.

Noted. No changes made because it is indeed "a focused history" to serve as the minimum.

c) Page 23. This section reads as though the option is for condom use OR one of the other prevention strategies. PrEP was administered in addition to counseling to use condoms.

Text reviewed and edited accordingly

d) Page 23. There are also data that condom failure rates are higher among MSM couples with anal sex, rather than among long-standing heterosexual couples practicing vaginal sex.

Noted. No change made as this kind of comparison of behaviors across populations is beyond the scope of the document.

e) Page 23. Helpful [HPTN 052 results]. You may also indicate that no data on MSM, nor among persons with multiple sex partners (who may have greater risk of acquisition, if there are STIs, or other factors).

The absence of data on transmission between men as added. A fuller explanation of results from the HPTN 052 trial is beyond the scope of this document.

f) Page 24. Box B2. Consider including recently incarcerated partner as potentially at high risk. It may be that even if they frequently (but don't consistently) use condoms with a partner at some substantial risk, PrEP should be offered.

Noted. No changes made because it is meant to provide a very brief set of questions to serve as the minimum.

g) Also, the first bullet after the "AND" statement seems to imply that all bisexual men would be eligible, when it is only for bisexual men who meet either the MSM or the hetero behavioral eligibility.

Text reviewed and revised accordingly

<u>Reviewer #3</u>

a) Box A1. The current phrasing is somewhat ambiguous with regard on who is actually not wearing the condom.

Text reviewed and edited accordingly

b) Box A2. Heterosexuals can and do engage in anal sex; this is risk is noted (in passing) in the text below.

Text reviewed. Anal sex added to HIV acquisition risk criteria for heterosexual women

c) Box B1. The eligibility criteria for MSM outlined above, although soundly based on the iPREX entry criteria, is predicated upon past behavior and does not incorporate future activity, risk or planned behavior such as divorce, sex tours etc.

Noted. No changes made as there is no evidence that future behavior is well predicted.

d) Box B2. The eligibility criteria for heterosexually active men and women outlined above, although soundly based on the Partners PrEP study criteria, is predicated upon past behavior and does not incorporate future activity, risk or planned behavior such as divorce, sex tours, transactional sex, etc.

Noted. No changes made as there is no evidence that future behavior is well predicted.

e) It also fails to take into account the similar behavioral and biological HIV acquisition risk for heterosexual woman engaging in anal receptive sex.

Text reviewed. Anal sex added to HIV acquisition risk criteria for heterosexual women

f) Page 25. We recommend getting HIV tested within 1 month after starting PrEP, and then going to q3 month testing for several reasons, including: 1) Rule out undetected HIV infection early; 2) Help with adherence issues when side effects are most likely to occur;

This is included in the text as an option for providers. These guidelines suggest an outer limit to the frequency of monitoring HIV status, adherence, and side effects (at least every 3 months) for safe use of PrEP. This guideline does not prevent clinicians from more frequent testing based on their clinical judgment about specific patients in their care.

g) 3) Pts should also be told to come back in for re-testing before "restarting" PrEP on their own if they have been off the study drugs or taking intermittently.

Text reviewed and edited accordingly

h) Page 32 I'd recommend that this [option for 1 month f/u]] be included as a formal recommendation, rather than a suggestion, although I know we don't have explicit data on this early check-in.

Noted. See response to f) above

i) Page 25. This [USPSTF HIV testing frequent recommendation] seems a little out of place here, as it is not specific to PrEP, and the issue with PrEP is different (i..e., resistance).

Text reviewed and edited accordingly

j) Page 26. [Figure 1] Do you also take into consideration pts who are on PEP or a very recent high risk exposure (>72 hours but <4 weeks, no symptoms yet)?

Text reviewed. No changes made to Figure 1 as it applies to all persons being HIV-tested before starting or for refills of PrEP medication

k) Page 29. [Table 7-Hepatitis B screening] Perhaps clarify that this is an idealized or simplified table, and that some pts may lose antibody (e.g., no HBc Ab but HBsAb and never vaccinated).

This is the table published by CDC's Division of Viral Hepatitis for clinician use. Therefore we have not amended it.

l) Page 37. But need to consider whether infection may have already occurred

Text reviewed and edited accordingly.

m) Page 38. My take-home message from this study is that adherence to less than daily dosing is poor, and reinforces that PrEP should be prescribed as daily.

Text reviewed and edited accordingly.

n) Page 40. [Project Respect counseling] How will you incorporate the Project Aware data?

This text will be reviewed and edited when data are published from the Project Aware trial.

o) Appendix 1. [HIV Test Tables] Any comment on sensitivity for oral fluid vs. blood?

Accepted and table revised accordingly

Reviewer #4

No comments requiring a response

Reviewer #5

a) On page 24, I question whether I would put any MSM with oral GC or CT on PrEP, so you may want to qualify the STD criterion in the absence of anal sex, unless you want a lot of oral-only MSM on PrEP

Noted. No change made since the recommendation is for sexually active MSM, many of whom have anal as well as oral sex.

Reviewer #6

No comments requiring a response